manipulation is selected from the group consisting of applying a hormone, applying a growth factor, applying an extracelluar matrix component, applying a virus, applying an electroporation, applying an antisense polynucleotide, applying a gene knock-out, applying a gene overexpression, applying a gene mutation, applying a cell fusion, and combinations thereof;

code for determining at least one of a plurality of features of a first component of said at least two of a plurality of components and at least one of a plurality of features of a second component of said at least two of a plurality of components;

code for determining a plurality of descriptors, wherein said code for determining a plurality of descriptors comprises code for performing principal component analysis on said plurality of descriptors, wherein said descriptors comprise at least one said plurality of features of said first component or at least one of a plurality of features of said second component and wherein at least one of said plurality of descriptors is formed by comparing features of said first component and said second component;

code for searching a plurality of descriptors obtained from a database to locate descriptors based upon one of said descriptors of said manipulation, said searching forming a plurality of located descriptors;

code for determining, based upon said located descriptors, properties of said manipulation based upon said located descriptors; and

a computer readable storage medium for holding the codes.

REMARKS

Applicants respectfully request reconsideration of the rejections set forth in the Office Action mailed on April 2, 2002. Claims 49-61 and 63-65 have been rejected and are now pending.

This amendment is to expedite prosecution and should not be construed as acquiescence in any ground of rejection. Applicants reserve the right to prosecute the originally filed claims in the future. A clean version of the amended claims with instructions for entry pursuant to 37 C.F.R. §1.121(c)(1)(i) is included above. A marked-up version of the amended claims pursuant to 37 C.F.R. §1.121(c)(1)(ii) is attached as Appendix I. The comments in the Office action are now addressed in turn.

Rejections under 35 U.S.C. § 103

Claims 49-61 and 63-65 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Biodx, Weaver et. al., Pauwels, and Weinstein or Biodx, Pauwels and Weinstein or Biodx, Singhvi,Pauwels, and Weinstein and further in view of Sunblad et. al. (J. Exp. Botany, 1998)za. This rejection is respectfully traversed as applied to the amended claims.

The teachings of Biodx, Weaver, Singhvi, and Pauwels have been discussed previously. More specifically, Biodx describes a computer-implemented method for,

> "performing high-throughput screening of the physiological response of cells to biologically active compounds and methods of combining high-throughput with high content spatial information at the cellular and sub-cellular level as well as temporal information about changes in physiological, biochemical, and molecular activities". (at Abstract)

In order to accomplish the desired high-throughput screening, Biodx relies upon a well defined combination of "multi-color luminescence reading, microfluidic delivery, and environmental control of living cells in non-uniform micro-patterned arrays" (at page 12, lines 7 – 8) that provides for "high throughput and high content screening of the physiological response of cells to biologically active compounds, which allows multiple types of cell interactions to be studied simultaneously" (at page 13, lines 5 – 7). Accordingly, Biodx specifically provides a well defined micro-array formed of any number of wells each of which can be specifically designed to bind cells having a particular characteristic. For example, at page 20 first paragraph of Biodx,

> "Modified non-uniform micro-patterned chemical arrays are produced by specific chemical modifications of the wells in the micro-patterned chemical array. The modified array of wells in the non-uniform micro-patterned chemical arrays may contain a variety of different cell binding molecules that permit attachment and growth of cells in the wells. The hydrophobic domains surrounding the wells on the base do not support the attachment and growth of the cells."

In this way, the array of wells presents a well defined and coherent group of living cells suitable the acquisition of data associated with biological activity based upon the application of any number and kind of externally applied manipulations thereof.

Biodx does not teach or suggest the use of image analysis techniques employing techniques such as multidimensional representations, frequency-based representations, multidimensional cluster analysis techniques, and the like. Accordingly, the Examiner admits

that none of the above cited references teach the use of principal component analysis upon the image components of the cellular manipulations. Therefore, the Exmainer cited, the secondary reference (Sundblad et al) in her 103(a) rejection of claims 49-61 and 63-65. Sundblad describes a "methodology for determination of mitotic index (MI) from apical meristems of conifers..." using, "vertical and controlled pressure for squashing..." that provides, "an interactive image analysis system for estimation of MI from preparations..." (at Abstract). Therefore, Sundblad is directed at using image analysis for the basis for determining a single variable (MI) based upon a "squashed" sample of apical meristem cells. In order to investigate "the potential for using image analysis as the basis for a fully automated system for the determination of MI, 14 morphometric and densitometric parameters for nuclei in squash images were recorded by the VISOR program. The relevance of the recorded parameters for determination of MI was investigated using two applications of principal component analysis (PCA) as described above." (at pg. 1752, second paragraph)

It is well known that principal component analysis (PCA) involves a mathematical procedure that transforms a number of (possibly) correlated variables into a (smaller) number of uncorrelated variables called *principal components*. The first principal component accounts for as much of the variability in the data as possible, and each succeeding component accounts for as much of the remaining variability as possible. Therefore, since the squashed samples of Sundblad presented a substantially incoherent and disorganized sample, Sundblad was forced to use PCA (or similar techniques) to verify the *use of image analysis* for evaluation of MI and not for the evaluation of reactions of living cells to externally applied manipulations as required by the invention. Since Biodx provided a well controlled and deterministic array of cells, it was unnecessary for Biodx to use PCA to evaluate the images presented by the cellular array in the manner required by Sundblad. Therefore, the Applicants believe that the teachings of Sundblad can not be combined with that of Biodx in support of the Examiner's 103(a) rejection.

In contrast, claim 56 recites

> "code for receiving one or more images of at least one of the plurality of cells that have been exposed to the manipulation;
>
> code for determining, from the one or more images, a first descriptor for a first component of at least one of the plurality of cells and a second descriptor for a second component of at least one of the plurality of cells; and
>
> code for analyzing the first and second descriptors to determine the effect of the manipulation on the plurality of cells, said code for analyzing the first and second descriptors comprising *code for performing principal component analysis on the first and second descriptors*"

and claim 63 requires

"code for determining a multiple descriptors comprises code for performing principal component analysis on the said multiple descriptors".

Therefore, claims 56 and 63 uses PCA for statistical evaluation of the various descriptors and not, as required in Sundblad, for determining the efficacy of using image analysis only (and therefore unrelated to the reactions of living cells to external applied manipulations). Accordingly, the Applicants believe that claims 56 and 63 are not obvious in view of the cited references and are therefore allowable.

Biodx describes analyzing cells wherein cells containing reporter molecules are scanned with a fluorescence microscope. The optical information is converted into digital data which is then used to determine the distribution, environment or activity of the labeled reporter molecules in the cells. A database is provided for storage and retrieval of data from each experiment. See, page 39, lines 6-11. Significantly, Biodx does not teach or suggest any methods for comparing data from one experiment with that from another.

In contrast to Biodx, claim 49 has been amended to require,

"code for determining a plurality of descriptors, wherein said code for determining a plurality of descriptors comprises code for performing principal component analysis on said plurality of descriptors, wherein said descriptors comprise at least one said plurality of features of said first component or at least one of a plurality of features of said second component and wherein at least one of said plurality of descriptors is formed by *comparing* features of said first component and said second component" (emphasis added)

For these reasons, withdrawal of the rejections is respectfully requested.

Conclusion

The Applicant respectfully maintains that all pending claims are in condition for allowance. Therefore, the Applicant respectfully requests a Notice of Allowance for this Application from the Examiner. Should any unresolved issues remain, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,
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APPENDIX I

MARKED UP VERSION OF AMENDED CLAIMS

49. (Thrice Amended) A computer program product for determining a property of a manipulation based upon determination of effects of said manipulation on at least two of a plurality of components of at least one of a plurality of cells, said computer program product comprising:

code for receiving one or more images of at least two of a plurality of components of at least one of a plurality of cells that have been exposed to the manipulation, wherein said manipulation is selected from the group consisting of applying a hormone, applying a growth factor, applying an extracelluar matrix component, applying a virus, applying an electroporation, applying an antisense polynucleotide, applying a gene knock-out, applying a gene overexpression, applying a gene mutation, applying a cell fusion, and combinations thereof;

code for determining at least one of a plurality of features of a first component of said at least two of a plurality of components and at least one of a plurality of features of a second component of said at least two of a plurality of components;

code for determining a plurality of descriptors, wherein said code for determining a plurality of descriptors comprises code for performing principal component analysis on said plurality of descriptors, wherein said descriptors comprise at least one said plurality of features of said first component or at least one of a plurality of features of said second component and wherein at least one of said plurality of descriptors is formed by [combining]**comparing** features of said first component and said second component;

code for searching a plurality of descriptors obtained from a database to locate descriptors based upon one of said descriptors of said manipulation, said searching forming a plurality of located descriptors;

code for determining, based upon said located descriptors, properties of said manipulation based upon said located descriptors; and

a computer readable storage medium for holding the codes.